

REMARKS

Claims 1-6, 9-13, 17, 30, 33-37, 44-52 and 54-63 were pending. Applicants have amended claims 1, 5, 6, 9, 12, 13, 30, 33, 34, 36, 37, 44, 46-48, 51, 52, 54-59, and 62-63 and cancelled claims 3, 4, 11, 17, 35 and 61. Further, claims 64-74 have been added. Accordingly, only claims 1, 2, 5, 6, 9, 10, 12, 13, 30, 33, 34, 36, 37, 44-52, 54-60, and 62-74 are pending and being examined.

Support for amended claims 1, 5, 6, 9, 12, 13, 30, 33, 34, 36, 37, 44, 46-48, 51, 52, 54-59, and 62-63 and new claims 64-74 may be found in the specification as originally filed. Accordingly, these changes do not involve new matter and Applicants respectfully request entry of these changes.

The amendment to claims 5, 6, 12, 13, 36, 37, 46, 51 and 54 merely corrects the dependency of the claim.

The amendment to claim 58 merely corrects the typographical error.

Support for amended claim 1 may be found in the specification as originally filed at page 6, lines 27-29; page 16, lines 20-27; page 26, lines 14-31; page 27, lines 1-2; page 30, lines 9-16; page 31, lines 9-16; and page 47, Example 1.

Support for amended claim 9 may be found in the specification as originally filed at page 16, lines 20-27; page 26, lines 14-31; page 27, lines 1-2; page 30, lines 9-16; and page 31, lines 9-16.

Support for amended claim 30 may be found in the specification as originally filed at page 27, lines 30-31 and page 28, lines 1-18.

Support for amended claim 33 may be found in the specification as originally filed at page 16, lines 1-3 and page 51, Example 3.

Support for amended claim 34 may be found in the specification as originally filed at page 16, lines 20-27; page 30, lines 9-16; and page 47, Example 1.

Support for amended claim 44 may be found in the specification as originally filed at page 21, lines 14-21; page 23, lines 16-17; and page 68, lines 28-30.

Support for amended claim 47 may be found in the specification as originally filed at page 7, lines 22-24; page 23, lines 16-17; and page 30, lines 9-16.

Support for amended claim 48 may be found in the specification as originally filed at page 21, lines 14-21; page 23, lines 16-17; and page 68, lines 28-30.

Support for amended claim 52 may be found in the specification as originally filed at page 29, lines 21-22.

Support for amended claim 55 may be found in the specification as originally filed at page 6, lines 27-29; page 26, lines 14-15; and page 29, lines 21-22.

Support for amended claim 56 may be found in the specification as originally filed at page 6, lines 27-29; page 26, lines 14-15; and page 29, lines 21-22.

Support for amended claim 57 may be found in the specification as originally filed at page 26, lines 18-19 and page 27, lines 24-26.

Support for amended claim 59 may be found in the specification as originally filed at page 26, lines 18-19 and page 47, lines 10-17.

Support for amended claim 62 may be found in the specification as originally filed at page 16, lines 20-27.

Support for amended claim 63 may be found in the specification as originally filed at page 7, lines 15-16; page 16, lines 20-27; page 26, lines 14-31; and page 27, lines 1-2.

Support for new claims 64 may be found in the originally filed specification at page 26, lines 17-31 and page 27, lines 1-2.

Support for new claim 65 may be found in the originally filed specification at page 20, line 12; page 22, lines 3-5; and page 41, lines 26-28.

Support for new claim 66 may be found in the originally filed specification at page 20, line 12 and page 41, lines 17-19.

Support for new claim 67 may be found in the originally filed specification at page 19, lines 21-31; page 22, lines 3-5; and page 41, lines 26-28.

Support for new claim 68 may be found in the originally filed specification at page 19, lines 21-31 and page 41, lines 17-19.

Support for new claims 69 may be found in the originally filed specification at page 19, line 31; page 20, lines 1-2; and page 41, lines 17-19.

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Support for new claim 70 may be found in the originally filed specification at page 19, line 31; page 20, lines 1-2; page 34, lines 16-19; and page 72, lines 17-19.

Support for new claim 71 may be found in the originally filed specification at page 35, lines 8-9; page 38, lines 7-9; page 41, lines 17-19 and SEQ ID NO:3.

Support for new claim 72 may be found in the originally filed specification at page 34, lines 16-19; page 35, lines 8-9; page 38, lines 7-9 and page 72, lines 17-19 and SEQ ID NO:3.

Support for new claim 73 may be found in the originally filed specification at page 35, lines 8-9; page 38, lines 7-9; page 41, lines 17-19 and SEQ ID NO:13.

Support for new claim 74 may be found in the originally filed specification at page 34, lines 16-19; page 35, lines 8-9; page 38, lines 7-9 and page 72, lines 17-19 and SEQ ID NO:13.

In accordance with the changes to the claims and the remarks that follow, Applicants respectfully request reconsideration of the outstanding rejections.

ITEM 1: APPLICANTS' AMENDMENTS

The Office acknowledges the amendments filed by the Applicants on September 11, 2005, and claims 1-6, 9-13, 17, 30, 33-37, 44-52 and 54-63, are pending.

ITEM 2: SPECIES ELECTION

The Office acknowledges the Applicants' election of the following species with traversal:

the alkylating agent is busulfan;
the first ligand is soluble CTLA4;
the second ligand is anti-CD40 antibody, and
the targeted condition is solid organ or tissue/cellular transplant.

The Office has indicated that in the interest of compact prosecution, and in view of enablement issues under 35 U.S.C. §112, first paragraph, the Office has extended the search to another alkylating agent, cyclophosphamide. Therefore, only claims 1-6, 9-13, 17, 30, 33-37, 44-52 and 54-63, are being examined in the instant application, to the extent that they read on the elected species. No response is due.

ITEM 3: TEXT OF SECTIONS OF TITLE 35 USC

The Office indicated that the text of sections of Title 35 USC, not included in this Action, can be found in a prior Action. No response is due.

ITEM 4: COMPLIANCE WITH SEQUENCE RULES

The Office indicated that including the amendments of September 11, 2005 to the instant specification brings the instant application in compliance with the sequence rules. No response is due.

ITEM 5: PRIORITY

At page 3 of the Office Action, the Office alleges that the priority application, U.S. Serial No. 60/264,528, filed January 26, 2001, does not provide sufficient written description for

- (a) "administering TDBM before, during and/or after a solid organ or tissue/cellular transplant";
- (b) "subsequently administering an alkylating agent (including busulfan)"; or
- (c) "administering an immunosuppressive composition before, during and/or after a solid organ tissue/cellular transplant", as currently claimed.

The Office has taken the position that the filing date of the instant claims is deemed to be the filing date of priority application U.S. Serial No. 60/303,142, filed July 5, 2001.

Applicants respectfully disagree that the priority application U.S. Serial No. 60/264,528, filed January 26, 2001, does not sufficiently describe the specific specification passages of (a)-(c) above for reasons of record.

The data supporting the passages above in U.S. Serial No. 60/303,142, filed July 5, 2001 may also be found in parent provisional application U.S. Serial No. 60/264,528, filed January 26, 2001. Applicants' support for "administering TDBM before, during and/or after a solid organ or tissue/cellular transplant" may be found in the skin graft experiments, at pages 4 and 5 of U.S. Serial No. 60/264,528. These experiments clearly describe administering TDBM on day 0 and on day 6. The skin graft was done on day 0. The data is shown in Figure 2A. Figure 2A clearly supports a claim of administering TDBM during and after a transplant. The claim of administering TDBM before the transplant can be inferred from the experiments described on page 5 of U.S. Serial No. 60/264,528, in which the mice which were administered TDBM on days 0 and 6 were re-challenged with skin transplants 100 days after the original transplant/protocol.

Applicants' support for "subsequently administering an alkylating agent" (now claimed as busulfan) is in the skin graft experiments at pages 4 and 5 and data is shown in Figure 2 of U.S. Serial No. 60/264,528. Herein, Applicants describe using busulfan on day 5.

Thus, in the skin graft experiments TDBM cells are administered on day 0, along with the skin graft, busulfan is administered on day 5, and TDBM cells are administered on day 6.

Regarding Applicants' support for "administering an immunosuppressive composition before, during and/or after a solid organ or tissue/cellular transplant", the immunosuppressive composition (now claimed as a costimulatory blockade comprising a combination of a first ligand that interferes with binding of CD28 to either CD80 or CD86, and a second ligand that interferes with binding of CD154 to CD40), is described at the bottom of page 2 of U.S. Serial No. 60/264,528 and is used in the skin graft experiments described at page 4 of U.S. Serial No. 60/264,528. The data is shown in Figure 2. Since the co-stimulatory blockade is described at the bottom of page 2 of U.S. Serial No. 60/264,528, as being administered on days 0, 2, 4, 6, 14, and 28, the use of the terms "before, during and/or after" is appropriate.

Accordingly, Applicants are entitled to the January 26, 2001 filing date and request that the Office withdraw the rejection.

ITEM 6: TITLE

The Office acknowledges Applicants' amendments to the Title and the Abstract.

ITEMS 7-10: REJECTION UNDER 35 U.S.C. §112 FIRST PARAGRAPH

Claims 57, 59 and 63 (New Matter)

At page 3 of the Office Action, the Office rejects claims 57, 59 and 63, under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter, which was not described in

the specification, in such a way as to convey to one skilled in the art, that the inventor(s) had possession of the claimed invention, at the time the application was filed.

Applicants respectfully disagree.

However, to further the prosecution of the subject application, Applicants have amended claims 57 and 59 to recite "wherein the alkylating agent is an alkylsulfonate and wherein the alkylsulfonate is busulfan." Further, Applicants have amended claim 63, to recite "wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazaposporines, nitrosoureas, and alkylating chemotherapeutic agents". Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claims 1-6, 9-13, 17, 30, 33, 44-52, 54 and 63 (Enablement)

At page 4 of the outstanding Office Action, the Office rejects claims 1-6, 9-13, 17, 30, 44-52, 54 and 63, under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification, in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully disagree. However in the interest of furthering prosecution, Applicants have amended claims 1, 9, 30 and 63, to include administration of a second dose of T cell depleted bone marrow cells, after administering an alkylating agent. Accordingly, in view of the aforementioned claim amendments, Applicants respectfully request that the rejection be withdrawn.

Claims 47-48 (Enablement)

At page 6 of the outstanding Office Action, the Office rejects claims 47-48, under 35 U.S.C. §112, first paragraph, alleging that while the specification is enabling for the specific mutant CTLA4 molecules, such as the L104EA29YIg molecule disclosed in the specification as filed, it does not reasonably provide enablement for any “CTLA4 mutant molecule,” to be employed as an immunosuppressive agent, in the instant claimed methods.

Applicants respectfully disagree for reasons of record.

However, in the interest of furthering prosecution of the subject application, merely to clarify, claims 47 and 48 has been amended to recite soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86. The claim amendment language in the aforementioned claims, tracks the language of the base independent claims from which the claims depend (either directly or indirectly).

For the record, Applicants traverse the rejection because Applicants provide methods for screening CTLA4 mutants for their binding capacity. (Example 9, pages 71-83, of the instant application). Further, Applicants provided examples of six CTLA4 mutant molecules, including their entire nucleotide sequences, and described the required functions for other members of the class of proteins, provided by the invention.

35 U.S.C. § 112, first paragraph, requires Applicants to teach how to make and use the invention, without undue experimentation. The law is clear. Applicants are not required to disclose every species encompassed by the claims (*In re Angstadt and Griffin*, 537 F.2d 498, 190 USPQ 215, 218 CCPA 1976)). Moreover, despite the fact that Applicants do not disclose every known CTLA4 mutant molecule, the identification of other species

in the class would not entail undue experimentation, because Applicants' disclosure outlines a number of different assays for the identification of CTLA4 mutant molecule as claimed. Practice of the claimed invention does not require undue experimentation.

In view of the preceding remarks, Applicants respectfully request that the Office reconsider and withdraw the rejection set forth in the Office Action.

Claims 50 and 56 (Enablement)

At page 9 of the outstanding Office Action, the Office has withdrawn previous rejection of claims 50 and 56, under 35 U.S.C. §112, first paragraph, in view of amended claims, deleting recitation of "L104EA29YIg," and Applicants' statements concerning the deposit under the Budapest Treaty and appropriate assurances. No response is due.

ITEM 11: REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Office alleges that claim 30 is indefinite in providing "busulfan prior to solid organ or tissue/cellular transplant", given Applicants' amended claims recite "(b) subsequently administering an alkylating agent...."

Applicants respectfully disagree. However in the interest of furthering prosecution, to clarify the invention, Applicants have amended claim 30 to recite "wherein one or both of the T cell depleted bone marrow so administered is administered before the transplant and wherein the busulfan is administered within any of (a) 24 hours prior to the solid organ transplant, (b) twelve hours prior to the solid organ transplant, or (c) six hours prior to the solid organ transplant."

Accordingly, Applicants respectfully request that the rejection be withdrawn.

ITEM 12: REJECTION UNDER 35 U.S.C. §102(e)

The Office has withdrawn the previous rejection under 35 U.S.C. §102(e), as allegedly anticipated by Sykes (U.S. Patent No. 6, 514,513), in view of the claim amendments filed by the Applicants on September 11, 2005. No response is due.

ITEM 13: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects claims 1-6, 9-13, 17, 30, 33-37, 44-52 and 54-63, under 35 U.S.C §103(a), as allegedly unpatentable over Sykes et al. (U.S. Patent No. 6,514,513), in view of art known practice and modes of administration of alkylating agents such as busulfan at various times to meet the needs of the patients, as acknowledged on pages 26-27 of the instant specification as evidenced by Andersson et al. (U.S Patent Nos 5,430,057 and 5,55,9148), Slattery et al. and Hassan et al.

Applicants respectfully disagree.

The Legal Standard for 35 U.S.C. §103

As stated in MPEP §2142, three (3) criteria must be met to establish a *prima facie* case of obviousness:

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the

claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon applicants' disclosure.¹

The teaching or suggestion to make the claimed combination, and the reasonable expectation of success, must both be found in the prior art, not in the Applicants disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. See *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Obviousness can not be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination.

The teachings of the references, their relatedness to the field of the applicant's endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. See *In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). When the references are in the same field as that of the applicant's invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them, as did the

¹ MPEP §2142, citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

applicant, must still be met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention. *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596,1600 (Fed. Cir. 1988).

The Examiner Has Not Established A *Prima Facie* Case Of Obviousness

The Examiner has not established a *prima facie* case of obviousness because not all of the three necessary criteria have been met. Therefore, as discussed below, the pending claims are patentable over the cited references.

A Discussion of the Cited References

Sykes et al., U.S. Patent No. 6,514,513 ('513)

Sykes discloses a method of promoting graft acceptance (e.g. skin graft), by a recipient mammal, wherein the graft is from a donor mammal of a second species. The method includes: administering to the recipient, an inhibitor, (e.g. either CTLA4Ig or anti-CD40 ligand mAB); administering low dose whole body irradiation; introducing hematopoietic stem cells (e.g., a bone marrow preparation) into the recipient mammal; and preferably, implanting the graft in the recipient. The hematopoietic cells are believed to prepare the recipient for the graft that follows, by inducing tolerance at both the B-cell and T-cell levels (Sykes at column 1, lines 49-52).

Sykes uses irradiation in the methods described (Sykes at column 22, lines 36-40; column 23, lines 15-19; column 24, lines 34-36; column 25, lines 9-12; and column 27, lines 52-55) but also suggests that busulfan may be used in lieu of irradiation, to create hematopoietic space. However, this suggestion is merely a wish. There is no reasonable

expectation of success if busulfan is substituted for whole body irradiation. This is because there is no direct correlation between the irradiation dosage and the busulfan dosage administered, to facilitate mixed hematopoietic chimerism. Additionally, the dosages of busulfan disclosed in the art at the time of the instant invention, correlated with the dosages of busulfan that one skilled in the art would use when treating neoplasias, and not dosages for inhibiting rejection, or reducing rejection, of solid organ transplant.

Andersson et al., U.S Patent Nos. 5,430,057 ('057) and. 5,559,148 ('148)

Patents '057 and '148 have identical disclosures, since the '148 patent is a continuation of the '057 patent. Accordingly, the '057 and the '148 patents are discussed together herein. The '057 and the '148 patents provide methods for use of parenteral formulation of busulfan, in the clinical treatment of human neoplasms, with therapy based on parenteral preparation alone, or in combination with other cytotoxic agent(s). Additionally, these patents provide formulations to increase solubility of busulfan, design of a chemically stable formulation of busulfan that is suitable for parenteral administration, and techniques to extract busulfan from blood, as well as pharmacokinetics of commercially available busulfan, and busulfan when solubilized in polyethylene glycol.

The '057 and the '148 patents fail to teach what the primary reference fails to teach, namely, the use of busulfan together with other agents of the claimed methods for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Moreover, these patents fail to teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the Sykes and the '057 and '148 patents does not render obvious the claimed methods.

Slattery et al., Therapeutic Drug Monitoring, 1998, 20:543-549

Slattery et al. provide methods for use of busulfan, to ablate marrow before hematopoietic stem cell transplantation, and the use of high levels of busulfan, in combination with cyclophosphamide, to treat patients with chronic myeloid leukemia. Further, Slattery et al. state that the therapeutic window for busulfan is narrow, and disease and graft-source dependent.

Slattery et al. fail to teach what the primary reference fails to teach, namely, the use of busulfan together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Further, Slattery et al. do not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the Sykes and Slattery et al. does not render obvious the claimed methods.

Hassan et al., Blood, 1994, 84:2144-2150

Hassan et al. provides methods for use of busulfan, in patients undergoing bone marrow transplantation, and evaluates the bioavailability of busulfan.

However, Hassan et al. fail to teach what the primary reference fails to teach, namely, the use of busulfan, together with other agents of the claimed methods, for facilitating mixed hematopoietic chimerism, and the effective dosage of busulfan for such use. Moreover, Hassan et al. fail to teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Accordingly, the combination of the Sykes and Hassan et al. references, does not render obvious the claimed methods.

THE LEGAL STANDARD HAS NOT BEEN MET BY THE OFFICE

The references in combination do not teach all of the claimed steps

The Examiner asserts that the claimed method is an obvious modification of the Sykes reference. However, as discussed above, the prior art references in combination does not teach or suggest all of the claim limitations, in the order claimed, namely, steps a-d of claims 1, 9, 34, 55, 56, 62 or 63.

Moreover, even if there were a suggestion or motivation to combine all elements of the claimed invention, there would not have been a reasonable expectation of success for the reasons which follow.

There was no suggestion to modify the prior art in order to obtain the claimed invention.

The Examiner's statement that it was within the skill in the art to make the modifications necessary to advance from the prior art to the claimed method is similar to an erroneous statement made in *Ex parte Levengood*.² In *Levengood*, the examiner stated that because the various aspects of the claimed process were individually known in the art (in the instant case, this is not true), the modifications of a prior art process necessary to arrive at the claimed invention were "well within the ordinary skill of the art at the time the claimed invention was made."³

The Board of Patent Appeals and Interferences reversed the Examiner's rejection because it was based on the wrong standard of obviousness: "At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art

² 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness.”⁴

The Examiner's reliance on what was within the skill in the art to support the obviousness of the modifications separating the prior art from the claimed invention is likewise an erroneous basis for finding the invention *prima facie* obvious over the cited art.

To establish a *prima facie* case of obviousness, the Examiner must present evidence that one skilled in the art would have been led to arrive at the claimed invention.⁵ Mere unsupported arguments cannot take the place of evidence.⁶

In this regard, Sykes merely suggests that other methods of creating hematopoietic space, e.g., administering hematopoietic space creating antibodies or drugs, e.g., cyclophasmide or busulfan, to the recipient, can be used (513 patent at column 5, lines 3-5). Without more, this statement cannot suggest the claimed invention. Merely desiring an end result does not constitute a specific modification of the prior art.

There is no evidence that any modification of the prior art would have led to a reasonable expectation of success in practicing the claimed invention.

It would not be enough to imply that, given the capabilities of those skilled in the art, it would have been obvious to try the claimed invention. In *In re O'Farrell*, the Federal Circuit gave examples of what would be obvious to try, but not obvious under 35 U.S.C.

³ *Id.* at 1301.

⁴ *Id.* (citations omitted).

⁵ *Id.*

⁶ *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658, 661 (CCPA 1979).

§103: "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."⁷ *O'Farrell* clarified the additional requirement for a reasonable expectation of success.

Sykes provides only a cursory statement of replacing irradiation with busulfan as a preparative regimen for bone marrow transplants (BMT) in connection with cancer treatment. This is very different from the claimed methods of inhibiting solid organ transplants. As the remaining cited references support, busulfan was well known in cancer treatment but never as a preparative treatment in connection with solid organ transplants. None of the cited references, alone, or in combination, provides guidance for modifying the methods to achieve therapeutically effective methods as claimed. Moreover, there was no reason to believe that busulfan dosages of the art as a preparative regimen for BMT would be extrapolatable for busulfan dosages for facilitating MHC in connection with solid organ transplants. Such cursory statements, however, are not equivalent to a reasonable expectation of success because there was no direction or guidance on how to proceed to achieve the prophetic goal based on the references.

In *In re Gangadharam*, the Federal Circuit reversed an obviousness rejection maintained by the Board of Patent Appeals and Interferences on the basis of a single prior art reference because the Patent and Trademark Office (PTO) had failed to meet its burden of proving a *prima facie* case of obviousness.⁸ The single cited reference stated that the result reported therein "offers a hopeful lead" for the therapeutic use claimed in the later application. The Federal Circuit stated that the Board's attempt to base their finding of a reasonable expectation of success for the claimed use on the one prior art reference "fell

⁷ 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

⁸ 889 F.2d 1101, 13 USPQ2d 1568 (Fed. Cir. 1989).

woefully short of its burden.”⁹

As in *Gangadharam*, the Examiner in the present case is basing the rejection under Section 103, of the claimed methods on the hopeful lead provided by the prior art. Like *Gangadharam*, the Examiner's attempt to base an obviousness rejection on the cited reference, i.e. *Sykes*, falls woefully short of its burden because data using irradiation as a preparative regimen for cancer therapy cannot teach the claimed method, for inhibiting rejection of a solid organ transplant in a subject.

The Examiner has not provided evidence that the prior art teaches or suggests *as a whole* the claimed methods. The claimed methods cannot be obvious over the cited references, because there was no suggestion regarding how to modify the prior art, in order to achieve the claimed methods. Moreover, even if it were obvious to try the combination of elements claimed, without a reasonable expectation of success, a *prima facie* case of obviousness cannot be made. It is therefore, respectfully requested that the rejection under 35 U.S.C. §103, be withdrawn, and that the claims be allowed.

**THE CLAIMED INVENTION POSSESSES UNEXPECTED ADVANTAGES
THAT THE CITED REFERENCES DOES NOT TEACH**

Applicants respectfully contend that the cited references do not render the claimed invention *prima facie* obvious. Furthermore, the alleged obviousness is rebutted by evidence of unexpected properties of the claimed invention (*In re Davies and Hopkins*, 475 F.2d 667, 177 U.S.P.Q. 381 (1973)).

⁹ *Id.* at 1569.

In addition to Applicants' previous showing, Applicants provide post filing confirmatory data showing that the methods of the invention possess superior properties. Specifically, Applicants provide the following:

1. Exhibit 1: L. Kean et al.

Here the authors show that nonmyeloablative preconditioning with busulfan (20mg/kg) coupled with costimulation blockade (CTLA4-Ig and anti-CD40L) can safely produce stable white blood cell (WBC) mixed chimerism and total replacement of the peripheral red cell compartment, resulting in a phenotypic cure of murine SCD. Furthermore, this cure is accomplished with fully major histocompatibility complex (MHC) mismatched donor marrow. Importantly, the hematologic cure that occurred with total replacement of the red cell compartment was accompanied by normalization of characteristic sickle organ pathology, indicating a total-body amelioration of disease.

2. Exhibit 2: Z. Guo et al.

The results of these studies demonstrate that the infusion of donor bone marrow together with busulfan and costimulation blockade (anti-CD40L mAb and CTLA4-Ig) induces hematopoietic chimerism and promotes the long-term survival of intestinal allografts transplanted into mice that have completed the treatment regimen. This long-term survival is associated with donor-specific hyporesponsiveness *in vitro* and deletion of donor-reactive T cells *in vivo*.

Exhibit 3: N. Shirasugi et al.

Treatment regimens consisting of costimulation blockade CB alone (CTLA4-Ig and anti-CD40L), CB and donor bone marrow cells (BMCs), and CB and donor splenocytes (DST) promote long-term allograft survival, but do not confer robust tolerance nor prevent chronic rejection in the face of a rechallenge with a donor skin graft. In contrast, a regimen consisting of CTLA4-Ig, anti-CD40L, donor BMCs, and a minimally myelosuppressive dose of busulfan produced stable donor-specific tolerance, and prevented both early and late cellular infiltration and chronic allograft vasculopathy, despite the rigorous rechallenge of a donor skin graft.

In view of the aforementioned discussion, Applicants respectfully request that the Patent Office reconsider and withdraw the rejection of claims 2-3, under 35 U.S.C. §103.

ITEM 14: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects claims 1, 9 and 33, under 35 U.S.C §103(a), as allegedly unpatentable over Sykes et al. (Sykes), in view of art known practice and modes of administration of alkylating agents such as busulfan, and in view of Larsen et al. (US Patent No. 5,916,560)(Larsen).

Applicants respectfully disagree.

Sykes was discussed above.

Larsen et al. teaches compositions and methods of inhibiting an immune response by using a combination of two agents, wherein the first agent blocks the CTLA4/CD28/B7 pathway, and the second agent blocks the gp39/CD40 pathway.

Larsen fails to teach what the primary reference, Sykes, fails to teach, namely, any amount of busulfan that would facilitate mixed hematopoietic chimerism. Further, Larsen does not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid organ transplants. Therefore, the combination of the Sykes and Larsen does not render obvious the claimed methods. Accordingly, Applicants respectfully request that the rejection be withdrawn.

ITEM 15: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects claims 1, 5, 9, 11, 12, 34-36, 44-52, 54, 56 and 60-61, under 35 U.S.C §103(a) as allegedly unpatentable, over Sykes et al. (Sykes), in view of art known practice and modes of administration of alkylating agents, such as busulfan, and in view of Peach et al. (US 20020182211) (Peach).

Applicants respectfully disagree.

Sykes was discussed above.

Peach teaches CTLA4 mutant molecules with mutations at position 29, and at position 104.

Peach fails to teach what the primary reference fails to teach, namely, any effective amount of busulfan that facilitates mixed hematopoietic chimerism. Further, Peach does not teach or suggest the use of busulfan for inhibition or reduction of rejection of solid

organ transplants. Therefore, the combination of the Sykes and Peach, does not render obvious the claimed methods. Accordingly, Applicants respectfully request that the rejection be withdrawn.

ITEM 16: UNEXPECTED ADVANTAGES

The Office acknowledges the arguments concerning unexpected advantages, but maintains the rejection.

ITEM 17: NO CLAIMS ALLOWED

The Office has indicated that no claims have been allowed in the instant application.

ITEM 18: THIS OFFICE ACTION IS MADE FINAL

The Office alleges that Applicants' amendments necessitated new ground(s) of rejections presented in this Office Action, and accordingly, has made this Office Action final.

ITEM 19: INQUIRIES

The Office indicated that any inquiries concerning this communication or earlier communications should be directed to Philip Gambel. Further, if attempts to reach the Examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants undersigned attorney invites the Office to telephone her at the number provided below.

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No other fee is deemed necessary in connection with the filing of this Amendment. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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